

EDITORIAL

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# Neural Interfaces for Bioelectronic Medicine

Dimitrios A. Koutsouras<sup>1\*</sup>  and Geert Langereis<sup>2\*</sup>

## Abstract

Bioelectronic medicine (BEM) is an emerging scientific field that aims to revolutionize the way we understand and treat disease by using electrical impulses for diagnosis and therapy. It is an interdisciplinary endeavour that draws on advances in microelectronics, information technology, materials science, and medicine, and it holds strong promise for addressing currently unmet medical needs. At its core, BEM seeks to develop implantable devices capable of modulating neuronal circuits and biological functions in a precise, targeted, and adaptable manner. Neural interfaces play a pivotal role within this therapeutic paradigm, as they must safely probe and interact with the nervous system while maintaining long-term stability and biocompatibility. This editorial introduces the papers published in our collection “Neural Interfaces for Bioelectronic Medicine”. The included works present the clinical landscape of neuromodulation, examine mechanisms of device failure and reliability, introduce electrode technologies with improved biocompatibility and selectivity, and explore the therapeutic potential of alternative neuromodulation strategies, such as ultrasound and magnetoelectric nanoparticle-based approaches, supported by computational models. Together, these contributions highlight both the opportunities and the challenges that must be addressed for bioelectronic medicine to fully flourish. They also identify the key technological advancements that will shape the future of neural interfaces and enable the next generation of bioelectronic therapies. We hope you enjoy this collection as much as we did.

We are pleased to welcome you to our collection on “Neural Interfaces for Bioelectronic Medicine”. Bioelectronic Medicine (BEM) is an emerging therapeutic paradigm that moves beyond traditional drug-based interventions by modulating neuronal activity and biological processes through implantable electronic devices (Koutsouras et al. 2024). By harnessing precisely targeted stimulation and sensing, BEM promises greater precision, selectivity, and adaptability than systemic pharmacological treatments, offering new possibilities for restoring health

in chronic and treatment-resistant conditions. Realising this potential requires the development of advanced neural interfaces capable of reliably crossing the biotic/abiotic boundary. These interfaces need to have excellent biocompatibility, biostability, and the ability to interrogate biology at the cellular level. Once such interfaces are established, closed-loop stimulation archetypes can be developed that are adaptive to guarantee selectively and long-term reliability. However, achieving this vision presents a fundamentally interdisciplinary challenge, requiring coordinated advances in microelectronics, material science, engineering, neuroscience and medicine for a seamless integration of bioelectronic devices with living tissue.

The aim of this collection is to present a snapshot of emerging trends in neural interfaces for therapeutic stimulation and sensing, with particular emphasis on developments shaping the next era of bioelectronic medicine.

\*Correspondence:

Dimitrios A. Koutsouras

dk2156@bath.ac.uk

Geert Langereis

g.r.langereis@tue.nl

<sup>1</sup>Department of Electronic and Electrical Engineering, University of Bath, Bath, UK

<sup>2</sup>Eindhoven University of Technology, Eindhoven, The Netherlands



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Its scope encompasses advances in electrode materials, fabrication techniques and device form factors, emerging paradigms in stimulation and biosensing, and innovative strategies for delivering bioelectronic medicine therapies.

The collection opens with a systematic review by Garrett W. Thrash and colleagues (Thrash et al. 2024), who surveyed the PubMed literature on clinical trials investigating neuromodulation as a treatment for drug-resistant hypertension (DRH). Their analysis highlights carotid body stimulation as a particularly promising approach, supported by several clinical studies reporting meaningful reductions in blood pressure. Spinal cord stimulation is also emerging as a potential therapy for DRH. Although early findings are encouraging, the authors emphasize that larger and more rigorous clinical trials are needed to establish its safety and efficacy. Following this, a comprehensive review by Ashley N. Dalrymple and colleagues (Dalrymple et al. 2025) examines the multifaceted challenges associated with implantable bioelectronic devices. The authors discuss how the foreign body response, along with mechanical, technological, and biological failure modes, can compromise device performance over time. They also outline current and emerging strategies for diagnosing these failure mechanisms and provide an overview of engineering and material-based solutions aimed at improving implant longevity and reliability.

The discussion then shifts to emerging applications of ultrasound-based neuromodulation. Weiguo Song, Stavros Zanos, and colleagues (Song et al. 2025) demonstrate that trans-spinal focused ultrasound (tsFUS) increases the von Frey threshold, indicating a reduction in mechanical hypersensitivity. Their findings suggest that tsFUS may offer a promising non-invasive approach for early-stage intervention in neuropathic pain. This is followed by a second study investigating the impact of focused ultrasound (FUS) applied to the superior mesenteric plexus (SMP) on metabolic function in a swine model of surgical stress (Song et al. 2025). The authors report that while SMP-FUS enhances intraoperative insulin sensitivity, it may simultaneously exacerbate post-operative hyperglycemia (POHG). These results underscore both the therapeutic potential and the complexities of ultrasound-mediated autonomic modulation, highlighting the need for further mechanistic and translational studies.

The discussion then moves to electrical stimulation paradigms. Soshi Samejima, Andrei Krassioukov and colleagues (Samejima et al. 2025) evaluate lumbosacral transcutaneous spinal cord stimulation (tSCS) in an individual with chronic motor-complete cervical SCI. After 30 sessions, the participant showed improved bladder compliance, better anorectal function, and reduced autonomic dysreflexia. Long-term tSCS also enhanced erectile function and sexual satisfaction, and concurrent

stimulation enabled voluntary leg movement. These results highlight the broad autonomic and motor benefits of lumbosacral tSCS and its potential as a viable therapeutic option after SCI. Next Matthew Johnson and colleagues (Kwaku et al. 2025) examined how renal nerve stimulation influences renal blood flow in a swine model by sweeping frequencies from 20 to 15,000 Hz. Low-frequency stimulation ( $\leq 100$  Hz) consistently produced sustained reductions in renal blood flow. Higher frequencies ( $> 100$  Hz) caused an initial drop that adapted over time during continued stimulation. Although kilohertz-frequency stimulation did not directly increase blood flow, it induced a notable carryover effect, reducing the sensitivity of the renal nerves to subsequent low-frequency stimulation. These findings highlight the frequency-dependent dynamics of renal neuromodulation. Then Rylie Green and colleagues (Ben et al. 2025) introduce a penetrating interfascicular electrode designed to enhance spatial selectivity in the peripheral nervous system. By exploiting the mechanical advantages of soft polymeric materials, their design mitigates the mismatch between rigid metal electrodes and compliant neural tissue. In an ex vivo sciatic nerve preparation, the device demonstrates high fascicular selectivity, highlighting its potential for precise peripheral neuromodulation. This is followed by the study of Loren Rieth and colleagues (Stump et al. 2025) on the stimulation stability of the Utah electrode array (UEA) optimized with Iridium Oxide (IrOx) coatings. They found that their metallization improves the stimulation lifetime of UEA compared to the BlackRock standard metallization technique.

The collection then shifts to computational modeling of magnetoelectric nanoparticles for neural sensing and activation. Valentina Galletta and colleagues (Galletta et al. 2025) present the first model to examine how nanoparticle concentration and spatial distribution affect peripheral nerve stimulation while accounting for the natural anatomical variability of nerve fibers. Their findings show that stimulation capability increases with higher nanoparticle concentrations, while variability at fixed concentrations arises from the stochastic placement of particles. The work further highlights the importance of optimizing stimulation parameters to target specific peripheral fibers, given the strong influence of axonal excitability on the neural response. Next, Giulia Caiani and colleagues (Caiani et al. 2026) assess the feasibility of using resonant magnetoelectric nanoparticles to detect the magnetic fields generated by the electrical activity of biological tissues. Their simulations show that magnetoelectric nanoparticles (MENPs) display high sensitivity to external magnetic field variations, with sensitivity depending non-linearly on core diameter.

Ellis Meng and colleagues (Li et al. 2026) conclude the collection with a critical and timely review of recent

advances in peripheral nervous system interfaces, with a particular emphasis on emerging strategies for targeting small-diameter nerves. Their article synthesizes the major ongoing challenges in the field and surveys the latest innovations in materials engineering, surface modification techniques, micro- and nanofabrication, novel closing and locking mechanisms, and the integration of wireless electronics, highlighting the technological pathways that are shaping the next generation of peripheral nerve interfaces.

Taken together, the contributions in this thematic issue illustrate the remarkable breadth and therapeutic potential of bioelectronic medicine. From clinical neuromodulation trials for drug-resistant hypertension to advances in ultrasound-based interfaces, electrical stimulation paradigms, next-generation implantable electrodes, and emerging magnetoelectric nanoparticle technologies, the collection highlights a field rapidly expanding its therapeutic, diagnostic, and technological frontiers. Yet the field remains in its infancy, with several important hurdles ahead. These include developing a deeper understanding of the complex interplay between biology and technology, engineering biocompatible materials with improved performance, designing devices capable of highly selective control of neural circuits, and establishing robust simulation frameworks to guide device optimization. Nevertheless, the progress showcased in this issue charts a clear course toward more targeted, less invasive, and more clinically impactful neurotechnologies capable of addressing a wide spectrum of unmet medical needs. We hope that this collection will stimulate continued innovation in the essential technologies needed to overcome current barriers, ultimately enabling emerging bioelectronic medicine to achieve its full therapeutic potential.

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#### Authors' contributions

Dimitrios A. Koutsouras and Geert Langereis supervised the work and wrote the manuscript.

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Not applicable.

##### Consent for publication

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##### Competing interests

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